Route-Dependent Severe Phenytoin Toxicity: A Comparison of Two Cases, Pharmacokinetic Analysis, and the Potential Role of Multiple-Dose Activated Charcoal

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Abstract

Phenytoin exhibits nonlinear, capacity-limited elimination governed by Michaelis–Menten kinetics, making toxicity highly sensitive to dose, route, and metabolic saturation. Comparative data on oral versus IV overdose remain scarce. We describe two phenytoin overdose cases illustrating distinct pharmacokinetic and clinical trajectories based on exposure route. Case 1: A 20-month-old girl accidentally ingested ~1,500 mg phenytoin (≈125 mg/kg), developing coma and seizures at a serum level of 218 µmol/L. She required intubation, gastric decontamination, and MDAC. Serial levels declined with clinical recovery (218.1 → 189.6 → 171.9 → 117.0 → 112.2 → 108.8 → 68.1 µmol/L), and she returned to baseline by day 4. Case 2: A 21-year-old woman with epilepsy received an inadvertent 5-g IV loading dose (≈111 mg/kg), resulting in ataxia, nystagmus, and depressed consciousness with a peak of 328.2 µmol/L. Managed supportively without MDAC, she remained stable but recovered slowly as serum levels declined (328.2 → 314.0 → 278.0 → 255.6 → 249.5 → 204.3 → 145.7 → 110.2 → 58.8 µmol/L), normalizing by day 7. Pharmacokinetic modeling confirmed classical Michaelis–Menten behaviour (Km ≈ 300 µmol/L) with route-dependent Vmax values: 4.9 µmol/L/h (IV) and 6.9 µmol/L/h (oral). The modeled effective half-life was ~55–60 h (IV) versus ~35–40 h (oral), shortening further below K_m as elimination reverted to first-order kinetics. The higher Vmax observed in the oral case may reflect MDAC-enhanced clearance through gastrointestinal adsorption and interruption of enterohepatic recirculation, although this association cannot be definitively established in this 2-case comparison.

Keywords: Phenytoin Toxicity; Quantitative Pharmacokinetic; Michaelis–Menten Elimination; Oral Phenytoin; IV Phenytoin; Multiple-dose Activated Charcoal (MDAC).

Introduction

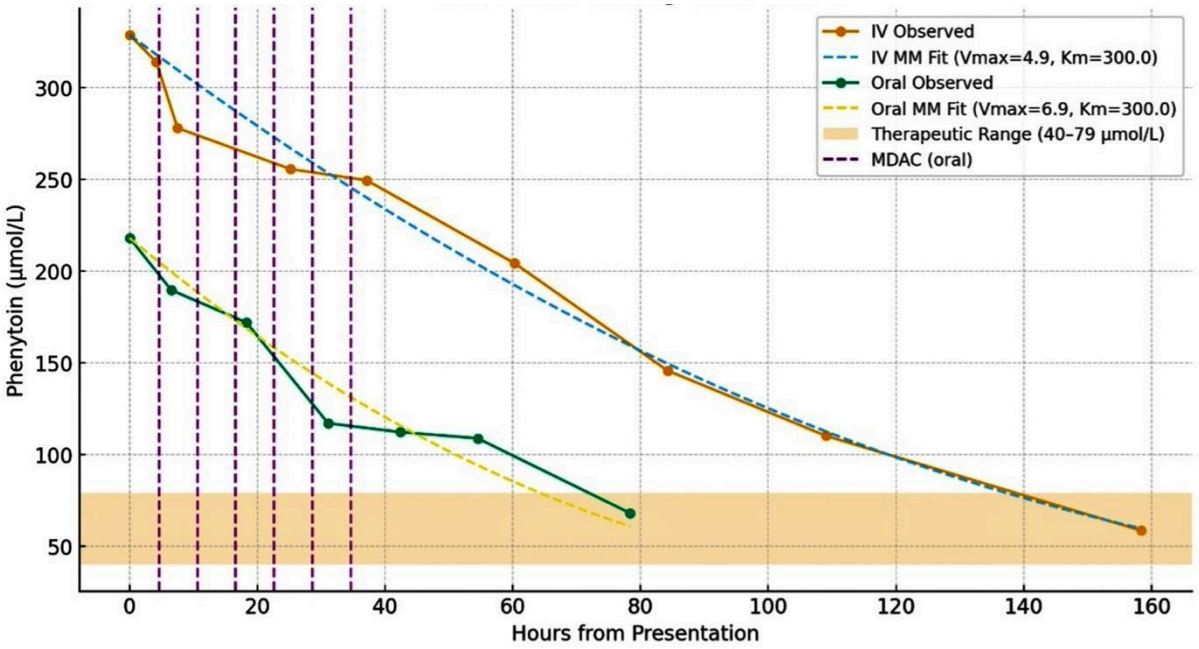
Phenytoin, a hydantoin derivative, remains a cornerstone anticonvulsant for generalized tonic–clonic and focal seizures.[1] Despite its utility, it has a narrow therapeutic index and nonlinear, capacity-limited elimination, making toxicity a well-recognized clinical concern.[1,2] Once hepatic hydroxylation becomes saturated, small dose increments can cause disproportionate rises in serum concentrations and toxic accumulation, even within therapeutic regimens.[3]

Phenytoin kinetics vary substantially by route. Oral formulations undergo extensive first-pass metabolism with a bioavailability of 70–90%, whereas intravenous (IV) administration bypasses this process and achieves near-complete systemic exposure.[4,5] Consequently, IV dosing carries greater risk of acute neurotoxicity and cardiovascular compromise if excessive or rapid.[2,3,6] Variability in toxicity thresholds further arises from differences in protein binding, tissue distribution, and elimination half-life—particularly in patients with hepatic dysfunction, hypoalbuminemia, or interacting drugs.[7] Clinically, toxicity presents with neurological, cardiovascular, and gastrointestinal features such as nystagmus, ataxia, dysarthria, altered consciousness, and, in severe cases, coma or arrhythmias.[2,3,6] Pediatric and adult presentations may differ owing to developmental variations in metabolism and drug distribution. Comparative analyses of oral versus IV toxicity remain rare, especially on a weight-adjusted basis. We report two such cases—a pediatric oral ingestion (1.5 g, 125 mg/kg) and an adult intravenous overdose (5 g, 111 mg/kg)—to explore how route of administration may influence phenytoin toxicokinetics and clinical course, while recognizing that age, baseline condition, and supportive care also differed between cases.

Case Report

Case one

A 20-month-old previously healthy girl presented after ingesting ~15 phenytoin tablets (100 mg each; ~1,500 mg or 125 mg/kg). Within two hours, she developed drowsiness, ataxia, and recurrent generalized seizures. On arrival, she was obtunded (GCS 7/15) with shallow respirations, requiring immediate intubation. Vitals showed tachycardia (160 bpm) and mild hypotension (85/60 mmHg), with horizontal nystagmus. Serum phenytoin was a total serum concentration of 218.1 µmol/L (therapeutic 40–79 µmol/L); serum glucose, electrolytes, and acid–base status were within normal limits at the time of seizure activity. Serum albumin was within the normal range; free phenytoin levels were not measured. She received multiple-dose activated charcoal (MDAC) administered as repeated doses according to institutional toxicology protocol, IV fluids (60 mL/h), and midazolam for seizure control [Figure 1]. Although seizures are not typical of phenytoin toxicity, in this case they were considered possibly related to extreme exposure after metabolic causes were excluded. Serial levels declined steadily—218.1 → 189.6 → 171.9 → 117.0 → 112.2 → 108.8 → 68.1 µmol/L—paralleling neurological recovery. She was extubated on day 3, fully alert by day 4, and discharged on day 5 without deficits.



Footnote: *Time zero represents hospital presentation for the oral ingestion case and completion of the IV infusion for the intravenous exposure case. The orange line shows observed IV concentrations and the blue dashed line the Michaelis–Menten model fit (Vmax = 4.9 µmol/L/h; Km = 300 µmol/L). The green line and yellow dashed line depict observed and modeled oral concentrations (Vmax = 6.9 µmol/L/h; Km = 300 µmol/L). The beige band (40–79 µmol/L) indicates the therapeutic range. Purple dashed lines mark the timing of multiple-dose activated charcoal administration in the oral case; the subsequent decline in concentrations was temporally consistent with enhanced gastrointestinal elimination, although causality cannot be established from this comparison. The model illustrates nonlinear, capacity-limited elimination, with apparent zero-order behavior at higher concentrations and transition toward first-order elimination as concentrations decrease.*

Figure 1: Observed and Michaelis–Menten Modeled Serum Phenytoin Concentrations Following Intravenous and Oral Overdose.

Case two

A 21-year-old woman with epilepsy and intellectual disability inadvertently received a 5 g IV loading dose (~111 mg/kg). Within hours, she developed marked drowsiness, slurred speech, and severe ataxia (GCS 6/15). Nystagmus was present, but vital signs and cardiac rhythm remained stable. Serum phenytoin was a total serum concentration of 328.2 µmol/L. Serum albumin was within the normal range; free phenytoin levels were not available. She was managed supportively with hydration and airway monitoring; MDAC was withheld due to

aspiration risk. Serial levels declined gradually—328.2 → 314.0 → 278.0 → 255.6 → 249.5 → 204.3 → 145.7 → 110.2 → 58.8 µmol/L—correlating with clinical improvement [Figure 1]. Over the next week, she regained responsiveness, coordination, and ambulation. Follow-up levels confirmed steady elimination consistent with nonlinear, saturation-limited kinetics.

As shown in Figure 1, observed versus modeled phenytoin concentrations were consistent with nonlinear, capacity-limited elimination characteristic of Michaelis–Menten kinetics.[8] Modeled parameters indicated a Km ≈ 300 µmol/L for both routes, aligning with adult data.[9-10] The Vmax was 4.9 µmol/L/h after IV and 6.9 µmol/L/h after oral exposure, with the higher value in the oral case possibly reflecting MDAC-associated enhancement of gastrointestinal adsorption and interruption of enterohepatic recirculation. However, this association cannot be confirmed from two cases alone. The estimated half-life was 55–60 h (IV) and 35–40 h (oral), shortening to 15–20 h once levels fell below Km, marking the shift from zero- to first-order elimination as enzyme saturation resolved.[4,9,10]

Discussion

These two cases suggest that the route of administration may influence phenytoin's toxicokinetic profile and clinical course. Despite a higher mg/kg ingestion in the pediatric case (125 mg/kg) compared to the adult IV exposure (111 mg/kg), the child recovered faster, whereas the IV overdose was associated with a more prolonged neurological recovery in this case series. This observation highlights a central pharmacologic principle: in capacity-limited systems such as phenytoin metabolism, systemic exposure rather than administered dose primarily determines toxicity.[4,9-11] Phenytoin elimination follows Michaelis–Menten kinetics ($V = Vmax \times C / [Km + C]$), where V represents metabolic rate, Vmax the maximal metabolic capacity, and Km the concentration at which metabolism proceeds at half of Vmax. Below Km (~300 µmol/L), clearance is first-order; above it, CYP2C9/19 saturation leads to zero-order kinetics.[8,12,13] This nonlinearity explains its narrow therapeutic window and the marked half-life prolongation at toxic concentrations.

These modeled parameters are consistent with classical nonlinear phenytoin elimination (Km ≈ 300 µmol/L) with route-dependent Vmax values—4.9 µmol/L/h (IV) vs. 6.9 µmol/L/h (oral)—consistent with literature.[13,14] The higher apparent Vmax observed in the oral case may reflect MDAC-enhanced clearance through intestinal adsorption and interruption of enterohepatic recirculation; however, this association cannot be definitively established from two cases alone.[2,3] The estimated half-life was 55–60 h IV versus 35–40 h orally, shortening to 15–20 h once concentrations fell below Km, typifying transitional kinetics.[13] MDAC may therefore have contributed to enhanced elimination, although a causal effect cannot be confirmed in this comparison.

Route-dependent divergence was further influenced by bioavailability, absorption, and physiology. Oral phenytoin undergoes first-pass metabolism (bioavailability ~ 70–80%), while IV dosing achieves immediate systemic exposure, which may more rapidly saturate metabolic pathways. In children, a higher hepatic clearance and shorter half-life—due to a larger liver-to-body-weight ratio and greater metabolic capacity—may have accelerated elimination, compounding MDAC's effect.[16] Reduced gastric acidity, slower transit, and variable CYP2C9/19 maturation also moderate pediatric absorption and peaks.[4,9,10] At toxic levels, protein binding becomes saturable, increasing the unbound fraction (10 → 25%) that freely crosses the blood–brain barrier, producing disproportionate neurologic symptoms.[2,3,6] Hence, free phenytoin levels correlate more closely with clinical status, especially in hypoalbuminemia or critical illness.[9-11] Distribution differences further shape kinetics: IV administration produces rapid CNS and hepatic delivery with redistribution sustaining plasma levels, whereas oral absorption aligns more smoothly with elimination.[1,2,6] Genetic polymorphisms in CYP2C9/19 may reduce clearance by up to 50%, explaining delayed recovery in slow metabolizers.[12-14] From a translational perspective, phenytoin toxicity illustrates how saturable metabolism, protein binding, and route-dependent exposure interact to shape clinical toxicity. Modeling of Vmax and Km enables clinical prediction of recovery time, optimal charcoal duration, and monitoring intervals.

This comparison involves only two cases with substantial differences in age, physiology, and baseline neurological disease; therefore, the observations should be considered hypothesis-generating and interpreted cautiously.

Conclusion

Route of administration may influence phenytoin's toxicokinetics and clinical outcome. IV overdose may lead to immediate enzyme saturation, zero-order elimination, and prolonged neurotoxicity, whereas oral

ingestion—limited by absorption and potentially aided by MDAC—may allow earlier reduction in serum concentrations and faster clinical recovery.

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